REMARKS ON THE DIFFERENTIAL DIAGNOSIS AND TREATMENT OF PERNICIOUS ANEMIA*

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SINCE the introduction of the modern methods of treating pernicious anemia, with their strikingly beneficial effects, one need not dwell upon the importance of recognizing the condition at the earliest possible moment. To overlook the diagnosis of a disease for which effective control methods are available, is obviously a regrettable error. In the eighty-nine years since Thomas Addison first described the disease, our diagnostic methods have improved to such an extent that pernicious anemia should be easily recognized in almost every case. In fact, with proper study, it is doubtful if there is any other disease in which the diagnosis can be made during life with a greater degree of accuracy. It is possible to go further and state that the clinician, having the advantage of a therapeutic test and repeated blood examinations during life, can surpass the pathologist in the accuracy of the diagnosis in this disease. This is because there are so many diagnostic features which are present with a great degree of constancy. In general, it may be said that if any person of middle age complains of the symptoms common to all the anemias, such as dyspnea, palpitation, recently developed pallor, weakness and ease of fatigue, and in addition has an achlorhydria, paresthesia of the hands and feet, and recurring attacks of glossitis, the diagnosis is indicated, even before the blood is examined.

After considering carefully the evidences of the disease in approximately 1,000 patients whom we have observed during the past eleven years at the Simpson Memorial Institute, it is clearly apparent that there are at least seven cardinal points of fundamental diagnostic significance. These are usually recognized or eliminated without difficulty; and, if all or even a majority of them are present, then the diagnosis of true Addisonian pernicious anemia is at once established. These are: (1) Achlorhydria; (2) Macrocytosis; (3) High color index; (4) The re-

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sponse to potent anti-pernicious anemia therapy; (5) Paresthesia; (6) Glossitis; (7) Leukopenia, or the absence of leukocytosis. Each of these will be discussed briefly.

1. *Achlorhydria.* There is no other finding, in any other recognized syndrome which occurs with greater constancy than the absence of "free" hydrochloric acid in the gastric secretions of patients with pernicious anemia. Moreover, all evidence indicates that this condition has always been present in these patients, and that it will invariably remain, regardless of treatment or the disappearance of symptoms referable to the gastrointestinal tract. The presence of hydrochloric acid in the gastric secretion, therefore, should eliminate at once the diagnosis of Addisonian pernicious anemia. In the entire field of clinical medicine there is no diagnostic fact which can be stated with a greater degree of finality. The question will at once be raised regarding those exceedingly rare instances in which it is reported that a patient supposedly had pernicious anemia but did not have an achlorhydria. The answer to this is, first, such an exception is one in many thousands and from a practical standpoint, therefore, it is not of clinical importance. Second, a technical error might well explain the discrepancy. And, third, the patient may have some other cause for the macrocytic anemia, such as sprue, disturbance of the gastrointestinal tract including liver disease, or one of several others. Finally, it should be stated that any conclusion regarding the state of the gastric juice should be based only upon observations made after the injection of histamin, which is the most powerful stimulus to gastric secretion known at present. This is emphasized because a patient may be suspected of having pernicious anemia and an absence of hydrochloric acid has been noted following the use of one of the several test-meals which have been utilized as diagnostic procedures for many years. More than once it has been possible to demonstrate the presence of hydrochloric acid in such patients when histamin has been used as a stimulus to gastric secretion.

2. *Macrocytosis.* All observers are in agreement that when an anemia is present, a macrocytosis is the most characteristic finding in the peripheral blood in patients with this disease. Moreover, this is the first characteristic change to occur when the anemia develops and the last to disappear when the blood approaches normal. By a macrocytosis is meant a mean corpuscular volume which exceeds 96 cubic microns and in some instances may be as great as 140 cubic microns. The actual

volume of the erythrocytes is the most satisfactory evidence of the presence or absence of a macrocytosis although satisfactory information may be obtained from measurement of the diameter of the cells by the Price-Jones technic. By this method it is possible to demonstrate in a macrocytic anemia, that a majority of the cells have a diameter exceeding the average normal measurement of 7.5 microns. It should be appreciated that the level of the erythrocyte count bears some relationship to the degree of macrocytosis. In general it may be said that its degree diminishes as the red blood cell count approaches normal, and that it is more pronounced as the anemia becomes more severe. An exception to this general statement is usually noted when the erythrocyte count falls to a million or less per cubic millimeter. Although the mean corpuscular volume may then be increased, the degree of this change may not be marked, possibly because fragmentation causes the appearance of many small erythrocytes which tend to reduce somewhat the average cell volume.

It is, of course, well known that macrocytic anemias occur which are due to causes other than those responsible for the production of pernicious anemia. Such an anemia may be present in:

1. Certain disorders of the digestive tract, such as gastric resection; "short circuiting" operations on the intestines or intestinal stenosis; liver disease; idiopathic steatorrhea; Dibothriocephalus infestation; and, chronic diarrhea due to various causes.

2. In association with various types of lymphoblastomas such as aleukemic leukemia and Hodgkin's disease.

3. In certain other anemias, as aplastic anemia, chronic hemolytic anemia, anemia of nephritis, anemia of pregnancy, and for a short interval following acute hemorrhage.

4. In myxedema.

5. In sprue and pellagra.

From a consideration of the above numerous causes of a macrocytic type of anemia, it is obvious that the presence of a macrocytosis is certainly not diagnostic of pernicious anemia. On the other hand, if a patient who is suspected of having pernicious anemia, is found to have a microcytic type of anemia, it is *exceedingly strong but not conclusive evidence* against Addisonian pernicious anemia. It should be remembered that a microcytic anemia may occasionally occur in pernicious anemia but in those rare instances when it is present, there is always some complication, the most common being hemorrhage, chronic infection, endocrine dis-

orders, or a dietary deficiency.

3. *Color Index.* What has been said about the macrocytosis in pernicious anemia from a diagnostic standpoint applies almost equally well to the color index which is usually 1.0 or greater. This is because there is a rough parallelism between the height of the color index and the size of the red blood cells. In general, it may be said that when they are largest, the color index is highest; and when they approach normal in size, the color index falls to approximately 1.0. In pernicious anemia during relapse, therefore, a color index of 1.0 or greater is to be expected. It is less than this only: (1) At the beginning of a spontaneous or therapeutically induced remission, when the red blood cells increase at a more rapid rate than the hemoglobin, and the color index, therefore, falls to 1.0 or lower; and (2) In the presence of the same complications which may cause a microcytosis, namely, prolonged bleeding, chronic infection, endocrine disturbances or a dietary deficiency.

4. *Response to Treatment.* The characteristic response to treatment may be considered under two headings: (1) Clinical evidence of improvement and (2) Changes in the blood. They both appear promptly that is, usually between three and six days after therapy is begun. At this time every evidence becomes apparent that the patient's condition is changing for the better. This is indicated by the disappearance of nausea and vomiting; the appetite is greatly improved; if fever is present, the temperature falls to narmal; the patient regains his strength rapidly and, in a relatively short time, is able to be up and about. There are very few conditions encountered in the practice of medicine which show such a remarkable and prompt response to specific therapy.

Indication of improvement in the blood is evidenced, first, by a striking increase in the number of reticulocytes, which begins between the third and sixth days after treatment, reaches the highest peak between the seventh to ninth days, and returns to normal at about the end of two weeks. With this change, the total erythrocyte count increases at about the rate of 200,000 to 400,000 red blood cells a week, depending upon the initial level of the erythrocyte count, the potency of the antipernicious anemia therapy, and the presence or absence of certain complications, such as infection. When these two characteristic responses occur it does not necessarily mean that the patient has pernicious anemia but it does indicate that either the disease is present or that the patient has a pernicious anemia-like blood condition which is seen in association with

certain disorders of the digestive tract, including liver disease, or the macrocytic anemia of pregnancy, Dibothriocephalus latus infestation, sprue and possibly pellagra.

The absence of such a response is clear-cut and almost conclusive evidence against the diagnosis of pernicious anemia, provided the red blood cell count is below three million and a liver extract of known potency has been administered parenterally in appropriate doses. It is true that the hematological response may be less in patients who have an acute infection or extensive arteriosclerotic changes, but it is never, under any circumstances, completely lacking.

5. *Paresthesia.* One of the most constant subjective evidences of this disease is the presence of numbness and tingling of all four extremities. In most textbooks it is stated that this complaint is present in about 80 per cent of these patients, but if specific information is obtained concerning this symptom, it will be found to be present in 90 per cent of the cases. It is encountered in patients who have involvement of the nervous system due to other causes, but in these conditions it is not so common to have it involve both the hands and the feet, as it almost uniformly does in pernicious anemia. The absence of this symptom does not eliminate the disease as a diagnostic possibility but indicates that a careful search should be made for some other explanation of the patient's condition.

6. *Glossitis.* Careful questioning of patients with pernicious anemia will reveal that about two-thirds of them give a history of having had attacks of glossitis, characterized by periodic recurrences of painful, sore tongue. The patients usually state that the condition almost invariably has remissions and exacerbations. The term "recurrent glossitis" is, therefore, appropriate. In addition, 42 per cent of our group had definite and easily recognizable atrophy of the papillae of the dorsum of the tongue, about which there could be no doubt. It is interesting to note that a patient's tongue may appear perfectly normal despite a history of severe recurrent glossitis and, on the other hand, there may be obvious atrophic changes without a previous history of symptoms referable to the tongue. Another observation in our experience has been that never has a patient with pernicious anemia been observed with an abnormally coated tongue when an anemia is present, regardless of the intensity of the symptoms. In general, it may be said that the existence of a coated tongue in a patient suspected of having pernicious anemia, casts considerable doubt upon the diagnosis.

Neither a history of glossitis nor atrophy of the tongue are conditions which are commonly encountered in clinical medicine and when present they should always suggest the possibility that the patient has pernicious anemia. It should be kept in mind, however, that similar tongue symptoms may occur in other conditions, such as sprue, pellagra, achlorhydric-microcytic anemia and various intestinal disorders.

7. *Leukopenia, or the Absence of Leukocytosis.* A diminished number of leukocytes is almost always observed in patients with pernicious anemia who have an anemia and are in a condition of relapse. This is true even in the presence of a severe pyogenic infection which ordinarily would evoke a leukocytic response. There is a tendency for the leukocytes, however, to increase in number at the beginning of a remission, either spontaneous or therapeutically induced. Moreover, it is a well known fact that if an infection occurs at that time, there may be an exaggerated response as indicated by a striking rise in the leukocytes to a level of 30,000 or 40,000 or greater. A leukopenia then is the rule during relapse. A leukocytosis which has been reported during this stage may well be an erroneous observation, which can be accounted for by the enumeration of nucleated erythrocytes in the counting chamber as leukocytes.

Splenomegaly

The older observers state that the spleen is palpable in perhaps 20 to 40 per cent of the cases. If this was the situation then, it is not true now, for it is rare to observe a spleen which is enlarged to a point where it is palpable beneath the left costal margin. Furthermore, the presence of a grossly enlarged spleen is strongly suggestive evidence that the patient has some cause other than pernicious anemia for the anemia. This is most frequently one of the lymphoblastoma group, such as aleukemic leukemia or Hodgkin's disease. Widespread liver disease, such as cirrhosis, may be associated with a macrocytic anemia and a moderately enlarged spleen. The anemia may be accounted for on the basis that there is inadequate storage of the erythrocyte maturing factor in the organ, and the splenic enlargement has been regarded as due to chronic congestion.

Remarks on the Treatment of Pernicious Anemia

Twelve years have now passed since the modern treatment of pernicious anemia was introduced by Minot and Murphy. During that

interval, ample opportunity has been afforded numerous observers to study the effects of various types of treatment and compare their results with those noted before the existence of specific therapy. Prior to 1926, the status of the treatment of pernicious anemia is well expressed in the following quotation from a monograph on pernicious anemia published by Dr. Frank Evans, just a few months before the liver treatment was introduced. He states: "The treatment of pernicious anemia is discouraging. No patient with true pernicious anemia has ever been cured. However successful any therapeutic procedure may have been at first, there comes a time when the patient does not react to any treatment, he gradually grows worse, and death ensues. Furthermore, no treatment has so far been suggested which can be shown to have prolonged life."

The conclusions regarding treatment which are expressed in this article, are based upon the observation of approximately 1,000 patients who have been treated by various methods of liver and stomach therapy between the years 1927 and 1938. They have been observed, at intervals, for periods varying between a few months and eleven years.

Of this group, approximately 10 per cent, or 100 patients, are dead. The fatal cases can be divided into two main groups of equal importance numerically: First, those who died of complications incident to extensive involvement of the nervous system; and, second, those who died of incidental and unrelated diseases. The first group still remains a challenge to the methods of treatment of pernicious anemia and calls for an improvement especially in the management of the spinal cord lesions. The second has no direct association with pernicious anemia but is concerned with the prevention and treatment of unrelated diseases, chiefly degenerative, which are a common cause of death of persons who belong to the middle age or elderly group. None of the patients in either group as far as could be determined, died of anemia *per se*.

The Effect of Treatment on Spinal Cord Lesions

Whereas one-half of the patients who died, did so as a result of complications incident to spinal cord changes, a very large proportion of these, either presented themselves for treatment for the first time when the neurological manifestations were advanced, or failed to follow instructions regarding treatment, and, as a result, the anemia failed to improve or there was a hematological relapse. Furthermore, many of them were treated before the more effective parenteral methods of administering

liver extract were in widespread use. It is conceivable that had these been used, better results would have been attained. A typical example of a patient for whom the most efficient therapy may accomplish very little, is as follows: One who when first seen, has an ataxic, spastic paraplegia, and is either confined to bed or has a great deal of difficulty in locomotion. Frequently the anemia is not severe as the red blood cell count may be in the vicinity of 3.5 million per cubic millimeter and the hemoglobin approximately 70 per cent. If there is not already a failure of function of the sphincter of the bladder when the patient is first observed, this eventually appears and results in a distension of the bladder with the development of a residual urine which almost always becomes infected. When this occurs, regardless of intensive therapy, it is exceedingly difficult to cause the blood to return entirely to normal limits, although it may improve considerably. There are two views concerning this partial failure of treatment. One is that any infection may inhibit the effectiveness of the antipernicious anemia therapy in some obscure way. The other is that such a patient may have two independent causes for the anemia, each of which contributes simultaneously to the observed level of the erythrocytes and hemoglobin. One cause is the usual mechanism which is believed to account for the anemia of pernicious anemia. As would be expected, this responds to liver or stomach therapy as indicated by a reticulocyte rise and some increase in the hemoglobin or red blood cells. The blood, although improved, does not return entirely to normal, because a second cause, namely chronic infection, continues to act regardless of the use of specific therapy. As long as the infection is present, therefore, the anemia will persist. Both considerations are hypothetical ones which explain the facts adequately, but the latter one appears to be more plausible.

Consideration of our present methods of treatment indicates the hope that the best results in the management of the nervous manifestations lie in the prevention of the degenerative changes, rather than anticipating that they can be improved or eradicated after they have once been established. Furthermore, it seems rational to speculate that if future investigation is to yield a helpful form of treatment, it will most likely be the result of research in the field of vitamin or closely allied therapy. It is not difficult to anticipate that in the near future, a specific deficiency will be found which accounts for the changes in the nervous system. Even if this be recognized, it must be admitted that it is hardly justifiable to assume

that a correction of such a deficiency will cause regeneration of the tracts in the spinal cord and hence restoration of function.

For the present, it may be said that there is a reasonable certainty of preventing the development or progression of spinal cord changes, if the red blood cells can be brought to a high normal level and maintained there constantly. Even this statement can be challenged as lacking in absolute scientific proof, but it must be conceded that it is more than just a fair assumption. We have never observed objective signs of cord changes develop or progress during a period when the blood has been uniformly normal. Having this knowledge, the intensive treatment of the anemia is certainly the obvious and logical principle upon which our treatment should be based.

The second and equally large group of fatalities requires only brief comment. These patients succumbed to the common causes of death in this age group, which goes to prove that our life expectancy tables are correct. Disregarding the fact that a patient of fifty may have pernicious anemia, the life expectancy for a healthy person of that age is only a limited number of years. It is to be anticipated that among a group of persons between forty-five and sixty-five years, some will develop hypertension, malignancy, arteriosclerosis, nephritis, pneumonia and other diseases, and encounter accidents which will prove fatal. This is precisely what occurred in our group of patients, and there was not the slightest evidence to indicate that there was anything but a coincidental association between the two disease conditions.

In conclusion, let me make several remarks about the treatment of pernicious anemia in general. Although the Committee on Standardization of Antipernicious Anemia Medication has done most creditable work, they would be the first to admit that the task is beset with difficulties. The chief one is that the units, as assigned to the products of different manufacturers, are not always interchangeable. For example, one product may contain fifteen units per cc. and another, one unit per 2 cc. yet if equal unit doses are given, the clinical results are not always the same. At present, therefore, the advice of the manufacturer should be followed and the result checked by frequent determinations of the red blood cell count. After all, the important thing is to give an adequate amount of the antipernicious anemia principle; there is no recognizable deleterious effect known to result from an excess of it.

It appears to be generally agreed that the most satisfactory treatment

of the disease at present is the intramuscular administration of liver extract. This has the advantage of eliminating all question of absorption from the gastrointestinal tract; the blood can be maintained at a normal level by an injection given at intervals of one to three weeks; and this form of treatment will be successful in patients in whom the oral method fails.

There is a possible, but unproven, danger that in using the highly refined products, some substances may be eliminated which are beneficial to the patient. Crude liver extract is known to contain the entire vitamin B complex and it is considered that this substance is related to the pathologic changes in the spinal cord. There are, however, no data which indicate that the addition of vitamin B influences favorably either the blood or changes in the nervous system.